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ORIGINAL ARTICLES

Pediatric hospitalizations due to SARS-CoV-2 infection with respiratory involvement

Hospitalizações pediátricas por infeção por SARS-CoV-2 com envolvimento respiratório

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ABSTRACT

Introduction: SARS-CoV-2 may have several clinical presentations infection in children, with some requiring hospitalization. The published evidence is still scarce regarding the best approach and treatment for these cases.

Objective: To describe pediatric hospitalizations due to SARS-CoV-2 respiratory infection in a tertiary centre.

Material and methods: Retrospective observational study of SARS-CoV-2 admissions with respiratory involvement in the pediatric ward of a tertiary hospital between March 2020 and April 2022. Inclusion criteria comprised pediatric patients (0-17 years) hospitalized for SARS-CoV-2 infection, with a length of stay >24 hours and respiratory infection code from the International Classification of Diseases. Data were collected through patients' electronic clinical records.

Results: A total of 32 patients were included, 53% of whom females, with a higher proportion of hospitalizations in the Autumn-Winter season (n=21, 66%) and a mean length of hospital stay of 7 days. The median age was 18 months (interquartile range 4-135 months), and the mean days of disease was 4. The main symptoms reported were fever (n=31, 97%) and cough (n=25, 78%). Comorbidities were present in 14 patients (44%), who presented the highest length of stay (mean of 10 days). Most patients (n=29, 91%) had performed blood workup and biochemical analysis, and 25% had a viral coinfection. Chest x-ray was performed in almost all patients (n=29, 91%), and CT-scan in 9%. Low-flow oxygen therapy was used in 50% of patients, and high-flow nasal cannula (HFNC) in 13%. One patient required intensive care. Long COVID symptoms were reported in 25% of the study sample.

Conclusions: In two years of pandemic, only 32 patients required hospitalization. Most required oxygen therapy, with good clinical course. HFNC appears to be safe and should be considered in the treatment of these patients. Patients with comorbidities seem to have prolonged and more severe disease.

Keywords: child; COVID-19; respiratory tract infection

RESUMO

Introdução: A infeção por SARS-CoV-2 apresenta diversas manifestações clínicas em idade pediátrica. Alguns doentes necessitam de internamento e a evidência científica é escassa quanto à sua melhor abordagem.

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Objetivo: Caracterizar os internamentos por infeção respiratória por SARS-CoV-2 em idade pediátrica num centro terciário.

Material e métodos: Estudo observacional retrospetivo de internamentos por infeção respiratória por SARS-CoV-2 num hospital terciário entre março de 2020 e abril de 2022. Os critérios de inclusão compreenderam doentes com COVID-19 em idade pediátrica (0-17 anos) internados, com um tempo de internamento >24 horas e código de infeção respiratória da *International Classification of Diseases*. Os dados foram recolhidos por consulta dos processos clínicos eletrónicos dos doentes.

Resultados: Foram incluídos 32 doentes (53% dos quais do sexo feminino), maioritariamente no outono-inverno (n=21, 66%) e com um tempo de internamento médio de 7 dias. A mediana de idades foi de 18 meses (variação interquartil 4-135 meses) e os doentes apresentaram-se com uma média de 4 dias de doença. Os principais sintomas foram febre (n=31, 97%) e tosse (n=25, 78%). Doentes com comorbilidades (44%) apresentaram o maior tempo de internamento (média de 10 dias). A maioria (n=29, 91%) tinha efetuado hemograma e avaliação bioquímica e 25% apresentou coinfeção vírica. Foi realizada radiografia torácica na maioria dos casos (n=29, 91%) e tomografia computadorizada em 9%. Foi utilizada oxigenoterapia de baixo fluxo em 50% dos doentes e cânula nasal de alto fluxo (CNAF) em 13%. Um doente necessitou de cuidados intensivos. Foram reportados sintomas de COVID longa em 25% dos doentes.

Conclusão: Em dois anos de pandemia, apenas 32 doentes necessitaram de internamento. A maioria recebeu oxigenoterapia, com boa evolução clínica. A CNAF demonstrou ser segura e deve ser considerada na abordagem a estes doentes. Doentes com comorbilidades parecem ter doença mais grave e prolongada.

Palavras-chave: criança; COVID-19; infeção do trato respiratório

INTRODUCTION

The clinical spectrum of coronavirus disease 2019 (COVID-19) varies from asymptomatic disease to severe pneumonia with acute respiratory distress syndrome and multiorgan dysfunction.[1] Among children and adolescents, the disease is usually less severe and has lower mortality compared to adults.[2]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of COVID-19. It is responsible for upper and lower respiratory tract infection, with fever, cough, rhinorrhea, and/or nasal congestion being common COVID-19 symptoms. [1] Dyspnea is also reported, but in a smaller number of cases.[1]

Children with underlying medical conditions are at increased risk of severe disease. For this reason, risk factors in this patient population should be addressed, and these patients should be closely monitored and treated early.[3]

Although a number of studies have been published focusing the management and treatment of COVID-19, their quality is heterogeneous.[4] Clinical trials involving pediatric patients are limited, resulting in a lack of specific treatment recommendations for this age group. Although most children with mild or moderate disease can be managed with supportive care alone, the current National Institutes of Health (NIH) guidelines for this age group are based on outcomes and safety data in the adult population.[5]

In patients with hypoxemia, the administration of oxygen via nasal cannula or mask is appropriate, with simultaneous monitoring of vital parameters and changes in the acid-base balance that could indicate clinical worsening.[7] In children with ineffective breathing and oxygen therapy, high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) should be used. The World Health Organization (WHO) recommends that HFNC should only be used in selected patients with hypoxemic respiratory failure.

The evidence for the use of pharmacological therapy in pediatric patients is scarce, and thereby it is only recommended in the most severe forms of COVID-19. However, decisions should be made on a case-by-case basis.[6,7]

The aim of this study was to describe pediatric hospitalizations due to SARS-CoV-2 infection with respiratory involvement in a tertiary referral hospital.

MATERIAL AND METHODS

Study design and setting

This was an observational retrospective study of pediatric patients hospitalized for SARS-CoV-2 infection with respiratory involvement in the pediatric ward of Centro Materno-Infantil do Norte (CMIN) of Centro Hospitalar Universitário do Porto (CHUPorto) between March 2020 and April 2022. Patient informed consent was waived, as the study only used data from electronic clinical records. Study results were reported following the STROBE statement for observational studies.

Participants, data collection, and variables

Inclusion criteria comprised pediatric patients (aged 0-17 years) admitted with a diagnosis of SARS-CoV-2 infection with respiratory involvement, with a length of stay >24 hours and at least one of the following main or secondary diagnoses according to the

International Classification of Diseases, 10th revision (ICD-10): J12.81, J13, U07.1. The absence of electronic clinical record data was the only predefined exclusion criterion, for potentially precluding the diagnostic classification.

Two strategies were adopted for retrieving the most thorough list of the hospitalizations compliant with inclusion criteria: 1) via administrative databases of CHUPorto's Data Department; and 2) via clinical databases of CHUPorto's Pediatric Department. After crosschecking all admission episodes, data were collected from the electronic records by the research team.

Data retrieved comprised demographic and administrative data (age, gender, hospital length of stay, International Classification of Diseases 10th Revision [ICD-10] diagnosis) and data regarding clinical presentation, workup, and treatment implemented during hospitalization.

The Wheeze, Air exchange, Respiratory rate and Muscle use (retraction) (WARM) score was chosen to assess the response to HFNC, as this is a respiratory scoring tool that is validated for measuring the effectiveness of bronchiolitis interventions. Scores were compared immediately before and after 24 hours of therapy.

Statistical analysis

Statistical analysis was performed using SPSS® version 28 (SPSS IBM, New York, NY, USA). Continuous variables were described through mean and standard deviation (SD) in cases of symmetric distribution and mean and interquartile range (25th centile; P25 – 75th centile; P75) in cases of non-symmetric distribution. Categorical variables were described using absolute and relative frequencies and compared using the Pearson's chi-squared test. One-sample proportion test was used for comparing the proportion of hospitalizations between seasons, and t-test for comparing the length of hospital stay between comorbidity subgroups. A p-value <0.05 was considered statistically significant for all inferential analyses.

RESULTS

All hospitalizations identified at CMIN between March 2020 and April 2022 as per inclusion criteria had adequate electronic clinical records and were included in the study, in a total of 32 cases (**Table 1**). The main cause for hospitalization identified was hypoxemia (n=15, 47%), followed by feeding problems (n=6, 19%). The median age of hospital admission was 18 months (minimum–maximum 1 month–17 years), with nine patients aged below 2 years, four patients aged between 2-10 years, and nine patients aged between 10-17 years. Hospitalizations of patients aged between 3 and 10 years were not reported.

Although not statistically significant (p=0.08), the number of hospitalizations was higher in Autumn-Winter (n=21; 66%) compared to Spring-Summer (n=11; 34%) months. The mean days of disease on admission was four (standard deviation [SD] 2), and the main symptoms were fever and cough (**Table 2**). About 44% of patients (n=14) presented comorbidities, the most frequent being pulmonary disease (50%), chromosomopathy (21%), renal disease (21%), and obesity (21%). The mean length of hospital stay was 10 days (SD 9) in patients with comorbidities and five days (SD 3) in patients without comorbidities, but this difference was not statistically significant (p=0.066).

Table 1 – Participants characteristics

Total admissions	32
Gender, n (%)	
Female	17 (53)
Male	15 (47)
Age (months)	
Median (P25-75)	18 (4-135)
Age groups, n (%)	
[0-2[years	19 (59)
[2-10[years	4 (13)
[10-17[years	9 (28)
Length-of-stay (days)	
Mean (SD)	7 (7)
Specific diagnosis, n (%)	
Pneumonia due to SARS- associated coronavirus	29 (91)
Pneumonia caused by Streptococcus pneumoniae	1 (3)
COVID19	3 (9)

Table 2 – Participants characteristics

Days of illness before admission, median (SD)	4 (2)
Clinical presentation, n (%)	
Fever	31 (97)
Cough	25 (78)
Dyspnea	14 (44)
Rhinorrhea	20 (63)
Vomiting	5 (16)
Diarrhea	11 (34)
Thoracic pain	5 (16)
Abdominal pain	2 (6)
Respiratory distress	14 (44)
Hypoxemia	15 (47)

Blood workup, specifically blood count, and biochemical assay were performed in 91% of patients (n=29), and blood gas analysis in 22% (n=7). Nasopharynx aspirate for identification of viruses besides SARS-CoV-2 was performed in 31% of patients (n=10), with positive result in 25% (n=8). Microbiological assessment of bacteria in sputum was positive in one patient, with identification of *Streptococcus pneumonia* (**Table 3**).

X-ray was performed in 91% (n=29) and computed tomography (CT) scan in 9% (n=3) of patients. Half of patients in this cohort (n=16; 50%) were treated with low-flow oxygen therapy (LFOT), with a mean of 4 days of disease at the time of LFOT initiation and a mean of 5 days of LFOT use (SD 4). HFNC was used in 13% of patients (n=4), with a mean of 7 days of disease at the time of HFNC initiation and a mean of 5 days of HFNC use (SD 5). The WARM score after 24 hours of HFNC was ≤3 for all patients, except for the only patient who required Pediatric Intensive Care Unit (PICU) admission and non-invasive ventilation. No patient required invasive ventilation.

Inhaled β-agonists were used in 31% of this patient population (n=10), inhaled steroids in 19% (n=6), systemic steroids in 31% (n=10), antibiotics in 41% (n=13), antivirals in 3% (n=1), and hydroxychloroquine in 3% (n=1) (**Table 4**).

After SARS-CoV-2 infection, eight patients (25%) reported symptoms not previously experienced, including dyspnea on exertion (n=4; 13%), persistent cough (n=2; 6%), and wheezing 6% (n=2; 6%). Three patients (9%) repeated the x-ray and four patients (13%) repeated the CT scan in outpatient setting, with normal findings.

Table 3 – Identified virus and bacteria (positive results)

	TOTAL
Virus, n (%)	8 (25)
RSV	4 (13)
Rhinovirus	2 (6)
Metapneumovirus	2 (6)
Bocavirus	2 (6)
Bacteria, n (%)	1 (3)
Streptococcus pneumoniae	1 (3)

Table 4 – Workup and treatment performed

Microbiology, n (%)	
Viral Nasopharyngeal	10 (31)
Sputum microbiology	1 (3)
Blood, n (%)	
Hemogram	29 (91)
Biochemical	29 (91)
Chest image, n (%)	
X-ray	29 (91)
CT scan	3 (9)
Treatments, n (%)	
Low-flow oxygen therapy	16 (50)
High-flow nasal oxygen	4 (13)
Inhaled β-agonists	10 (31)
Inhaled steroids	6 (19)
Systemic steroids	10 (31)
Antibiotics	13 (41)
Antiviral	1 (3)
Hydroxychloroquine	1 (3)

DISCUSSION

Disease severity and risk factors

A total of 32 pediatric patients with respiratory symptoms were hospitalized in CMIN of CHUPorto between March 2020 and April 2022, 17 of whom required LFOT or HFNC. This is in line with published data reporting a less severe COVID-19 disease in children.[8] Similarly to Götzinger *et al.* and Preston *et al.*, chronic medical conditions were found to be risk factors for severe disease in the present study.[9,10] Although the mean days of hospital stay was higher in children with compared to without comorbidities, the difference was not statistically significant, which might be explained by the small sample size and thus low statistical power of this study. Interestingly, no hospitalizations between the ages of 3 and 10 years were observed in this study.

Main symptoms

The main symptoms reported by patients in this cohort were fever and cough. Although chest pain was less frequent, three of five

patients reporting this complaint required HFNC, and one LFOT. In addition, the presence of signs or symptoms of lower respiratory tract infection at presentation was found to be a significant risk factor for PICU admission.[9]

Laboratory workup

Most patients in this cohort performed blood count and biochemical assay. Although the laboratory blood test is unspecific, it may provide useful information for risk stratification. Viruses other than SARS-CoV-2 were detected in the respiratory samples of eight patients (25%), a higher percentage than reported by others. The rate of viral coinfection was 5% in a European multicentre cohort study and 12% in a study from the Geneva Pediatric COVID Group.[9,11] However, these studies differ from the current one in that they also included patients managed in outpatient setting and not just in inpatient setting. In the referred multicentric European study, patients with viral coinfection were significantly more likely to require PICU admission, respiratory support, or inotropic support.[9] In the present study, all patients with viral coinfection required LFOT but not HFNC or PICU admission. Furthermore, nasopharyngeal aspirate was not performed in patients with more severe disease, limiting the conclusions that can be drawn.

Chest x-ray and CT scan

The role of imaging assessment in pediatric patients with known or suspected COVID-19 pneumonia is still debatable, as there are no distinctive features of this disease compared to other viral infections. The American College of Radiology states that neither chest radiography nor chest CT should be used in the first-line diagnostic assessment of suspected COVID-19 infection.[12,13]

As for other pneumonias, chest x-ray is not indicated for most pediatric patients with COVID-19 not requiring hospitalization. For patients with moderate-to-severe disease, chest x-ray is usually indicated to establish the baseline imaging assessment and investigate alternative diagnoses.[12] The sample enrolled in this study included only inpatients, which can explain the high rate of chest x-rays performed (91%). Radiological follow-up should be avoided after discharge, except in cases of clinical worsening.[12] In the present study, most patients had mild involvement, with only three patients having repeated the chest x-ray.

CT imaging is usually performed in patients with severe clinical presentation.[14,15] In this study, three patients had performed CT scan. One was a 17-year-old with obesity (BMI 39.44 kg/m^2), who presented with hypoxemia, dyspnea, and chest pain. Another was also a 17-year-old who presented with the same respiratory symptoms and had recurrent wheezing in childhood. The last patient was 12 years old, obese (BMI 27 kg/m^2), and presented with hypoxemia and chest pain. The second and third patients required HFNC, but none was transferred to PICU. After discharge, the second patient repeated the CT scan, with no no abnormal findings. An obese patient (BMI 46.33 kg/m^2) in this cohort who had not performed CT scan during hospitalization did it in ambulatory setting, with normal findings. Improvement or normalization of CT findings is described in the literature.[14,15]

LFOT and HFNC

According to PICU guidelines for COVID-19 infection, children with COVID-19 and hypoxemia should begin supplemental oxygen therapy by low-flow nasal cannula when oxygen saturation (SpO_2) is <90%.[16] Half of patients (n=16; 50%) in this cohort required oxygen therapy, a higher percentage compared to the one found in a study with 1099 patients in China, where it was provided to 41.3% of patients.[1]

PICU COVID-19 guidelines also state that children with the infection with persistently increased breathing work and hypoxemia should be escalated to HFNC, if available.[16] HFNC was provided to four patients in this study. In recent years, HFNC has been used in patients with acute hypoxemic respiratory failure. However, the extent of requirements associated with COVID-19 outcomes, such as decreased requirement for tracheal intubation or lower risk of escalation to non-invasive or invasive mechanical ventilation, is still unknown.[17] At CMIN, the vast experience with HFNC in children with acute respiratory distress syndrome allowed to apply this procedure to COVID-19 patients.

At CMIN, HFNC is usually initiated in patients with a WARM score ≥5 (moderate-to-severe respiratory distress), which was observed in two female and two male patients with a mean age of 14.5 years in this study. Two patients were obese (BMI 46.33 kg/m^2 and 27 kg/m^2, respectively), one had a polymalformative syndrome, and the fourth was apparently healthy with only history of recurrent wheezing in childhood. All these patients presented with fever, three (75%) with thoracic pain, three (75%) with dyspnea, and three (75%) with cough. WARM score after 24 hours of HFNC therapy improved in all patients, except in the one who required PICU admission for persistent hypoxemia and shortness of breath.

The early parameters of all the patients treated with HFNC were 1 L/kg/min of air flow and 40% of FiO_2, followed by FiO_2 titration to achieve SpO_2 > 92%. The maximum air flow used was 50 L and 95% of FiO_2. Two patients discontinued HFNC after 24 hours, of whom one required noninvasive ventilation (NIV) and the other failed to adapt to the interface and was changed to high oxygen concentration through non-rebreathing face mask with reservoir bag. A third patient required treatment for four days, and a fourth patient, an obese child with 46.33 kg/m^2 of BMI, for 12 days.

Pharmacological therapy

Although no longer recommended, one patient in this cohort was treated with lopinavir/ritonavir and hydroxychloroquine in March 2020, according to recommendations of the National Health Service (SNS) at the time.[5,18] It was a patient with Angelman syndrome, with chronic hypoxemic respiratory failure in the context of bronchiolitis obliterans.

The safety and effectiveness of dexamethasone or other corticosteroids in the treatment of COVID-19 have not been

sufficiently assessed in pediatric patients. According to the National Institutes of Health (NIH) guidelines, dexamethasone is only recommended for patients requiring HFNC, NIV, mechanical ventilation, or extracorporeal membrane oxygenation. There is not enough evidence to recommend either for or against the use of inhaled corticosteroids.[5] In this cohort, 10 patients (31%) were treated with systemic steroids, including those who required HFNC.

Long COVID

After discharge, all patients were reassessed in Pediatric Pulmonology or Immunology consultation. After COVID-19 infection, a quarter of patients in this study (25%) developed symptoms never experienced before, which is in agreement with a meta-analysis reporting an incidence of long-COVID of 25.24%.[19] In that meta-analysis, the main symptom was dyspnea on exertion, followed by persistent cough and wheezing, symptoms that children infected by SARS-CoV-2 are at greater risk of developing.[19]

The present study has limitations that should be acknowledged. Firstly, it was a retrospective descriptive study, with data collection relying on adequate ICD-10 coding and adequate clinical records. Secondly, it included a small sample size, which hampers the conclusions that can be drawn, due to low statistical power. Lastly, WARM score, which aimed to measure the clinical response to HFNC, is only validated for bronchiolitis.

CONCLUSIONS

In two years of COVID-19 pandemic, only 32 patients required hospital care in the present tertiary referral hospital. Most required oxygen therapy (LFOT or HFNC), with good clinical course. Only one patient required PICU admission, with further adequate clinical course. The use of HFNC was safe and associated with clinical benefits, validating this procedure as a legitimate treatment option for children with COVID-19 infection. Patients with comorbidities seem to have prolonged and more severe disease, thereby requiring an individualized approach.

AUTHORSHIP

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